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(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING MAGNESIUM STEARATE

(57) Abstract: The invention relates to the use of magnesium stearate to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein the active ingredient substance is susceptible to chemical interaction with the carrier. An inhalable solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with lactose, (b) a carrier and (c) magnesium stearate is also provided together with uses thereof and methods related thereto.

WO 2005/004845 A1

PHARMACEUTICAL FORMULATIONS COMPRISING MAGNESIUM STEARATE

The present invention relates to solid pharmaceutical formulations which comprise an active ingredient drug substance, a carrier and magnesium stearate. The invention also relates to the use of magnesium stearate to inhibit or reduce chemical reaction or degradation of an active ingredient substance in the presence of a carrier. The invention also relates to the use of magnesium stearate for the stabilisation of an active ingredient drug substance in the presence of a carrier.

An important requirement of pharmaceutical formulations is that they should be stable on storage in a range of different conditions. It is known that active ingredient substances can demonstrate instability to one or more of heat, light or moisture and various precautions must be taken in formulating and storing such substances to ensure that the pharmaceutical products remain in an acceptable condition for use over a reasonable period of time, such that they have an adequate shelf-life. Instability of a drug substance may also arise from contact with one or more other components present in a formulation, for example a component present as an excipient.

It is usual practice in the pharmaceutical art to formulate active ingredient substance with substances known as excipients which may be required as carriers, diluents, fillers, bulking agents, binders etc. Such excipients are often used to give bulk to a pharmaceutical formulation where the active ingredient substance is present in very small quantities. Such substances are generally chemically inert. Over prolonged storage times, or under conditions of extreme heat or humidity, and in the presence of other materials, such inert substances can, however, undergo or participate in chemical degradation reactions.

Carrier substances that are commonly utilised in solid pharmaceutical formulations include reducing sugars, for example lactose, maltose and glucose. Lactose is particularly commonly used. It is generally regarded as an inert excipient.

However, it has been observed that certain active ingredient substances may undergo a chemical reaction in the presence of lactose and other reducing sugars. For example, it was reported by Wirth *et al.* (*J. Pharm. Sci.*, 1998, **87**, 31-39) that fluoxetine hydrochloride (sold under the tradename Prozac®) undergoes degradation when present in solid tablets

with a lactose excipient. The degradation was postulated to occur by formation of adducts via the Maillard reaction and a number of early Maillard reaction intermediates were identified. The authors conclude that drug substances which are secondary or primary amines undergo the Maillard reaction with lactose under pharmaceutically relevant conditions.

The present inventors have found that, under accelerated stability conditions, certain inhalable active ingredient substances also undergo degradation in the presence of lactose, possibly also via the Maillard reaction.

Some inhalable dry powder pharmaceuticals are sensitive to moisture, as reported, for example in WO 00/28979 (SkyePharma AG). The presence of moisture was found to interfere with the physical interaction between a carrier and a drug substance and thus with the effectiveness of drug delivery. Such interference with physical interactions between a carrier and a drug substance is distinct from chemical instability resulting from degradation.

A commonly used excipient in solid pharmaceutical formulations is magnesium stearate, which is often included as a lubricant. WO00/28979 (SkyePharma AG) describes the use of magnesium stearate in dry powder formulations for inhalation to improve resistance to moisture and to reduce the effect of penetrating moisture on the fine particle fraction (FPF) of an inhaled formulation. WO00/53158 (Chiesi) describes a powder for use in a dry powder inhaler including an active ingredient and a carrier, wherein the carrier includes a lubricant, which may, for example, be *inter alia* magnesium stearate.

WO 96/23485 (Coordinated Drug Development Ltd), WO01/78694 and WO01/78695 (Vectura Limited) each describes a powder for use in a dry powder inhaler including an active ingredient particles and carrier particles, wherein the carrier includes an additive which is able to promote release of the active particles from the carrier particles. Possible additive materials include amino acids, phospholipids, fatty acids and derivatives of fatty acids such as salts and esters, including *inter alia* magnesium stearate

We have now surprisingly found that chemical interaction of active ingredient substance and carrier may be inhibited or reduced by the presence of magnesium stearate.

In a first aspect therefore the present invention provides the use of magnesium stearate to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein said active ingredient substance is susceptible to chemical interaction with said carrier.

The invention also provides the use of magnesium stearate to inhibit or reduce chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising the active ingredient substance and a carrier, wherein said active ingredient substance is susceptible to chemical interaction with said carrier. The chemical stability of the active substance in the formulation during long term storage may thereby be improved.

In a second aspect the present invention provides a solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with a carrier, (b) a carrier and (c) magnesium stearate.

In a third aspect the present invention provides a method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing magnesium stearate with said active ingredient substance and said carrier. The invention also provides a method of inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing magnesium stearate with said active ingredient substance and said carrier.

Pharmaceutical formulations that have been prepared according to the present invention have greater chemical stability than the corresponding formulations without said ternary agent.

In the context of the present invention magnesium stearate may be referred to as a ternary agent. 'Ternary agent' is used herein to mean a compound used in a formulation in addition to the active ingredient drug substance or substances (the 'primary' agent) and a bulk carrier material or materials (the 'secondary' agent). In some circumstances more than one ternary agent may be used. Optionally, further substances, possibly named 'quaternary agents', may also be present, for example as a lubricant. Any particular ternary or quaternary agent may have more than one effect.

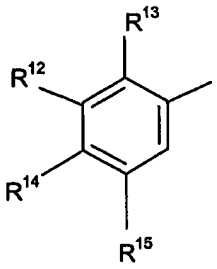
The invention finds particular application in formulations in which the carrier is a reducing sugar, for example lactose, maltose or glucose (for example monohydrate glucose or anhydrate glucose). In a preferred embodiment, the carrier is lactose. Alternative carriers include maltodextrin.

The optimal amount of magnesium stearate present in a particular composition varies depending on the identity of the active ingredient drug substance present, the sizes of the particles and various other factors. In general, magnesium stearate is preferably present in an amount of from 0.1 to 20% w/w based on the total weight of the composition. More preferably the magnesium stearate is present in an amount of from 0.2 to 10% w/w based on the total weight of the composition. Still more preferably, the magnesium stearate is present in an amount of from 0.3 to 6% w/w, for example from 0.5 to 4% w/w.

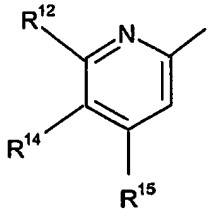
The active ingredient substance is typically present in an amount of from 0.01% to 50% w/w based on the total weight of the composition. Preferably, the active ingredient substance is present in an amount of from 0.02% to 10% w/w, more preferably in an amount of from 0.03 to 5%w/w, for example from 0.05% to 1% w/w, for example 0.1% w/w.

Preferably, the active ingredient drug substance is one which includes a primary or secondary amine group. Thus for example the drug substance may contain the group Ar-CH(OH)-CH_2-NH-R.

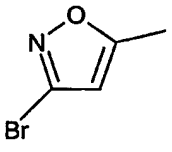
The group Ar may for example be selected from a group of formula (a) (b) (c) or (d):



(a)

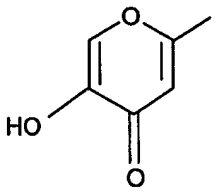


(b)



(c)

and



(d)

wherein R^{12} represents hydrogen, halogen, $-(CH_2)_qOR^{16}$, $-NR^{16}C(O)R^{17}$, $-NR^{16}SO_2R^{17}$, $-SO_2NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-OC(O)R^{18}$ or $OC(O)NR^{16}R^{17}$,
and R^{13} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{12} represents $-NHR^{19}$ and R^{13} and $-NHR^{19}$ together form a 5- or 6- membered heterocyclic ring;

R^{14} represents hydrogen, halogen, $-OR^{16}$ or $-NR^{16}R^{17}$;

R^{15} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{16}$, $-NR^{16}R^{17}$, $-OC(O)R^{18}$ or $OC(O)NR^{16}R^{17}$;

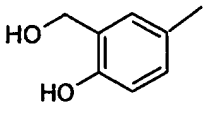
R^{16} and R^{17} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{16}R^{17}$, $-SO_2NR^{16}R^{17}$ and $-OC(O)NR^{16}R^{17}$, R^{16} and R^{17} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{18} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

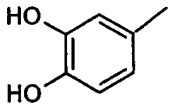
q is zero or an integer from 1 to 4.

In a particular embodiment, the group Ar is as defined above except that R^{12} is not hydrogen.

Within the definitions of (a) and (b) above, preferred groups may be selected from the following groups (i) to (xxi):



(i)



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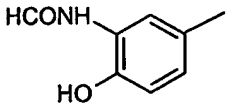

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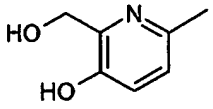

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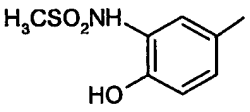

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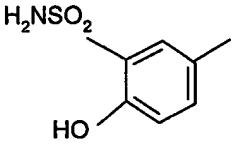
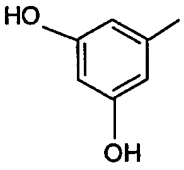


(vi)

(vii)



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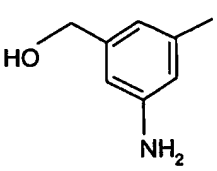

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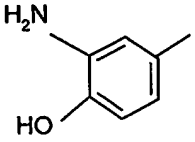
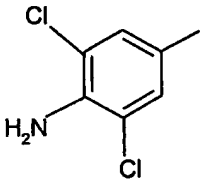
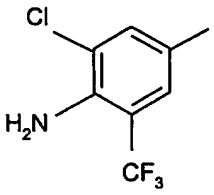


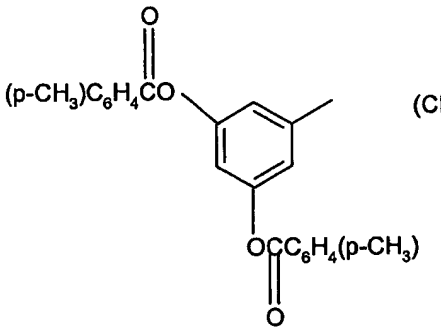
(x)



(xi)



(xii)



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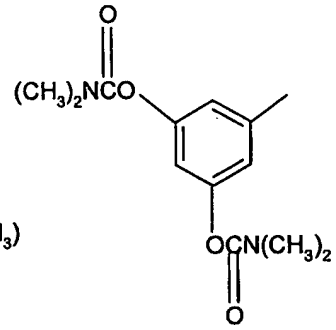

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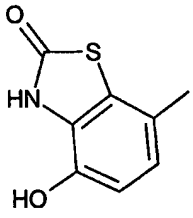
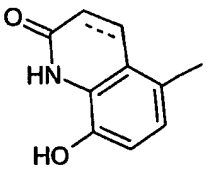


(xv)



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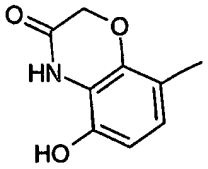

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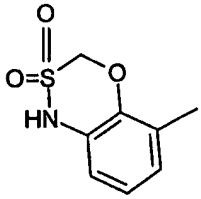

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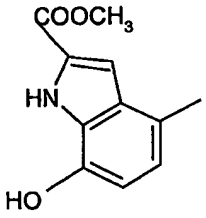

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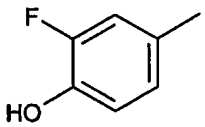

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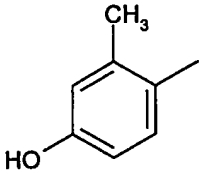

(xxi)

wherein the dotted line in (xvi) and (xix) denotes an optional double bond.

In a particular embodiment Ar represents a group (i) as defined above.

In another embodiment Ar represents a group (iii) as defined above.

The group R preferably represents a moiety of formula:

-A-B-C-D

wherein:

A may represent $(CH_2)_m$ wherein m is an integer from 1 to 10;

B may represent a heteroatom, e.g. oxygen, or a bond;

C may represent $(CH_2)_n$ wherein n is an integer from 1 to 10; and

D may represent an aryl group, e.g. an optionally substituted phenyl or pyridyl group.

Drug substances which may be formulated in accordance with the present invention include those described in International Patent Applications WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762, and WO 2004/039766.

Specific drug substances which may be formulated in accordance with the present invention include:

3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide for example as its cinnamate salt;

3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide;

4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and

4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol

and salts, solvates and other physiologically functional derivatives thereof.

Other drug substances which may be formulated in accordance with the present invention include salmeterol, (R)-salmeterol, salbutamol, (R)-salbutamol, formoterol, (R,R)-formoterol, fenoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerobuterol, reproterol, bambuterol and terbutaline and salts, solvates and other physiologically functional derivatives thereof.

The active ingredient drug substance may be in the form of a free acid or base or may be present as a salt, a solvate, or other physiologically functional derivative. Salts and solvates which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable.

Suitable salts for use in the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, phenylacetic, substituted phenylacetic eg. methoxyphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, mandelic, cinnamic, substituted cinnamic (for example, methyl, methoxy, halo or phenyl substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid and α-phenyl cinnamic acid (E or Z isomers or a mixture of the two)), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

A physiologically functional derivative of a drug substance may also be used in the invention. By the term "physiologically functional derivative" is meant a chemical derivative of a compound of having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters, for

example compounds in which a hydroxyl group has been converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

The active ingredient drug substance is most preferably a selective long-acting β_2-adrenoreceptor agonist. Such compounds have use in the prophylaxis and treatment of a variety of clinical conditions, including diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Formulations to which the present invention may be applied include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier and the magnesium stearate ternary agent as well as any other accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient, lactose, magnesium stearate and any other accessory ingredients, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules. The active ingredient drug substance may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine

the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include sterile powders, granules and tablets intended for dissolution immediately prior to administration. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

The invention finds particular application in dry powder compositions, in particular in dry powder compositions for topical delivery to the lung by inhalation.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715 or EP0237507). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing an active compound. Preferably, the strip is sufficiently flexible to be wound into a roll.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably

2-5μm (mass mean diameter, MMD). Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient substance as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. In general, the particle size of the carrier, for example lactose, will be much greater than the drug substance within the present invention. It may also be desirable for other agents other than the active drug substance to have a larger particle size than the active drug substance. When the carrier is lactose it will typically be present as milled lactose, for example with a mass mean diameter (MMD) of 60-90μm and with not more than 15% having a particle diameter of less than 15μm.

The magnesium stearate will typically have a particle size in the range 1 to 50μm, and more particularly 1 - 20μm, e.g.1-10μm.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example a beta-agonist may be used in combination with one or more other therapeutic agents selected from anti-inflammatory agents (for example a corticosteroid, or an NSAID,) anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines.

Suitable corticosteroids include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the

17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1).

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention further provides the use of an inhalable solid pharmaceutical formulation according to the invention for the manufacture of a medicament for the treatment of diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis). The invention also provides a method for treating asthma, chronic obstructive pulmonary diseases (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection upper respiratory tract, or rhinitis, including

seasonal and allergic rhinitiscomprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation according to the invention.

In a further aspect, the invention provides a method of preparing a solid pharmaceutical preparation comprising combining in one or more steps: (a) an active ingredient substance susceptible to interaction with a carrier, (b) a carrier and (c) magnesium stearate.

Examples

Test compound

In the following examples, the drug compound, "Compound X" was the cinnamate salt of 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}-butyl)benzene-sulfonamide. The synthesis of compound X is described in Examples 45 and 46 in WO 02/066422.

Method

Preparation of blends

Lactose monohydrate was obtained from Borculo Domo Ingredients as BP/USNF form. Before use, the Lactose Monohydrate was sieved through a coarse screen (mesh size 500 microns) to deaggregate the material. Compound X was micronised before use in an APTM microniser to give a MMD (mean mass diameter) of from 2 to 5 microns.

Magnesium stearate was obtained from Peter Greven with MMD < 10 microns and used as supplied.

The magnesium stearate was combined with lactose monohydrate and blended using either a high shear mixer (a QMM, PMA or TRV series mixer) or a low shear tumbling blender (a Turbula mixer) to provide a ternary agent/drug premix, hereinafter referred to as blend A.

Final blend B was obtained by first pre-mixing an appropriate quantity of blend A with compound X and then blending that blend A/compound X premix with further blend A in a weight ratio appropriate to provide blend B containing the magnesium stearate in the required quantity, as indicated in Table 1 and Tables 2 and 3 below. The quantity of magnesium stearate in Tables 2 to 3 is the amount by weight of magnesium stearate present as a percentage of the total composition. The final concentration of compound X in the blends was 0.1% w/w calculated on the basis of the weight of free base drug present.

For use in example 2, the blended composition was transferred into blister strips or the type generally used for the supply of dry powder for inhalation and the blister strips were sealed in the customary fashion.

The quantity of the various materials used in the various blends are shown in Table 1:

Table 1

Excipient	Mass of excipient	Mass of compound X	Mass of lactose
None	-	0.14g	99.86g
2% Mg stearate	2.00g	0.14g	97.86g
1% Mg stearate	1.00g	0.14g	98.86g
0.5% Mg stearate	0.50g	0.14g	99.36g

0.14g of compound X in the form of the cinnamate salt was used to provide 0.1g of compound X free base.

Decomposition conditions

The blends prepared as described above were subjected to accelerated decomposition conditions in a controlled atmosphere stability cabinet. In the tables below, the conditions to which the blends were subjected are given with reference to the temperature and the % relative humidity, for example 30/60 is 30°C and 60% relative humidity (RH). Samples were analysed for decomposition products after the time periods indicated in the tables.

Analysis of purity of blends after subjection to decomposition conditions

LC analysis was conducted on a Supelcosil ABZ+PLUS column (150 x 4.6mm ID), 3 micron, eluting with water containing 0.05% trifluoroacetic acid (solvent A) and acetonitrile

containing 0.05% v/v trifluroacetic acid (solvent B), using the following elution gradient: time 0 = 90% solvent A, 10% solvent B; 40 mins = 10% solvent A, 90% solvent B; 41-45 mins 90% solvent A, 10% solvent B, . Flow rate was 1ml/min and the column temperature was 40°C. Detection was carried out by UV at 220nm with a HP1100 series detector model G1314A-VWD. The area under the LC trace curve for the total impurities was compared with the total area under the curve, to give the %area/area figures given in Tables 2 and 3 .

Results

Example 1: Comparison of compound X / lactose blends comprising magnesium stearate with controls

Table 2:

Blend Details	Timepoint	Condition °C/%RH	Total Impurities (% area/area)
Compound X with Lactose only	Week 2	30/60	5.0
		40/75	8.9
	MN6	30/60	12.7
		40/75	17.4
Compound X with Lactose and 2% Magnesium Stearate	Week 2	30/60	3.4
		40/75	5.3
	MN6	30/60	4.1
		40/75	5.1

Example 2: Comparison of compound X / lactose blends comprising 0.5%, 1.0% and 2.0% magnesium stearate filled into blister strips with controls

Table 3:

Blend Details	Timepoint	Condition °C/%RH	Total Impurities (% area/area)
Compound X with Lactose only	Initial	Initial	3.7
	MN1	25/60	3.7
		30/60	4.3
		40/75	6.3
Compound X with Lactose and 0.5% Magnesium Stearate	Initial	Initial	3.2
	MN1	25/60	3.0
		30/60	3.0
		40/75	3.8
Compound X with Lactose and 1.0% Magnesium Stearate	Initial	Initial	3.2
	MN1	25/60	3.2
		30/60	3.3
		40/75	3.8
Compound X with Lactose and 2.0% Magnesium Stearate	Initial	Initial	3.1
	MN1	25/60	3.2
		30/60	3.3
		40/75	3.7

CLAIMS

1. Use of magnesium stearate to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein said active ingredient substance is susceptible to chemical interaction with said carrier.

2. Use of magnesium stearate to inhibit or reduce chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising the active ingredient substance and a carrier, wherein said active ingredient substance is susceptible to chemical interaction with said carrier.

3. Use as claimed in claim 1 or claim 2 wherein the carrier is a reducing sugar.

4. Use as claimed in claim 3 wherein the carrier is lactose.

5. Use as claimed in any one of claims 1 to 4 wherein the magnesium stearate is present in an amount of from 0.1 to 20% w/w based on the total weight of the composition.

6. Use as claimed in any one of claims 1 to 5 wherein the active ingredient substance is present in an amount of from 0.01% to 50% w/w based on the total weight of the composition.

7. Use as claimed in any one of claims 1 to 6 wherein the drug substance is one which includes the group Ar-CH(OH)-CH_2-NH-R.

8. Use according to claim 7 wherein said drug substance is selected from:

3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide;
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide;
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and
4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,
or a salt, solvate or physiologically acceptable derivative thereof.

9. Use as claimed in any one of claims 1 to 8 wherein the solid pharmaceutical formulation is for administration by inhalation.

10. Use as claimed in any one of claims 1 to 9 wherein the solid pharmaceutical formulation comprises two or more active ingredient substances.

11. An inhalable solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with lactose, (b) a carrier and (c) magnesium stearate.

12. An inhalable solid pharmaceutical formulation as claimed in claim 11 further comprising one or more of the features described in any one or more of claims 3 to 10.

13. An inhalable solid pharmaceutical formulation as claimed in claim 11 or claim 12 wherein the active ingredient substance is 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide; or a salt, solvate or physiologically acceptable derivative thereof, and the carrier is lactose.

14. A method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing magnesium stearate with said active ingredient substance and said carrier.

15. A method of inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing magnesium stearate with said active ingredient substance and said carrier.

16. A method as claimed in claim 14 or 15 further comprising one or more of the features described in any one or more of claims 3 to 10.

17. Use of an inhalable solid pharmaceutical formulation as claimed in claim 11 to 13 for the manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease or rhinitis, including seasonal and allergic rhinitis.

18. A method for treating asthma, chronic obstructive pulmonary disease (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease, or rhinitis, comprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation as claimed in claim 11 to 13.

5

19. A method of preparing a solid pharmaceutical preparation comprising combining in one or more steps: (a) an active ingredient substance susceptible to interaction with a carrier, (b) a carrier and (c) magnesium stearate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007666

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, L	WO 03/088943 A (BULSARA PALLAV ARVIND ; GLAXO GROUP LTD (GB); ROCHE TREVOR CHARLES (GB) 30 October 2003 (2003-10-30) page 2, line 22 - line 28 page 5, line 23 - page 6, line 34 page 7, line 34 - page 8, line 4	1-19
X	WO 00/28979 A (SKYEPHARMA AG ; MUELLER WALZ RUDI (DE); KELLER MANFRED (DE)) 25 May 2000 (2000-05-25) page 9, line 5 - line 15 page 16, line 15 - page 17, line 15 page 21; table 1	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2004	25/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Muller, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/007666

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/007666

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03088943 A	30-10-2003	WO 03088943 A1	30-10-2003
WO 0028979 A	25-05-2000	AT 233550 T	15-03-2003
		AU 756852 B2	23-01-2003
		AU 6457899 A	05-06-2000
		CA 2347856 A1	25-05-2000
		WO 0028979 A1	25-05-2000
		CN 1326341 T	12-12-2001
		CZ 20011553 A3	12-09-2001
		DE 59904488 D1	10-04-2003
		DK 1131059 T3	30-06-2003
		EP 1283036 A1	12-02-2003
		EP 1131059 A1	12-09-2001
		ES 2192866 T3	16-10-2003
		HU 0104226 A2	28-02-2002
		JP 2002529498 T	10-09-2002
		NO 20012346 A	26-06-2001
		NZ 511527 A	25-10-2002
		PL 347640 A1	22-04-2002
		PT 1131059 T	31-07-2003
		RU 2221552 C2	20-01-2004
		SK 6322001 A3	07-01-2002
		US 6645466 B1	11-11-2003
		ZA 200103627 A	09-05-2001